Allen B. Cohen, M.D., Ph.D.
Associate Professor of Medicine
Temple University Health Sciences Center
3420 North Broad Street
Philadelphia, Pa. 19140

The Genetic Defect in Alpha-1-Antitrypsin Deficient Patients.

The purpose of these experiments is to examine the products which result from the interaction of alpha-1-antitrypsin with enzymes in order to determine the mechanism of inhibition. Recent evidence from the investigators' and other laboratories has suggested that enzymes combine with alpha-1-antitrypsin in a manner analogous to the way in which they combine with other protein substrates; however, the alpha-1-antitrypsin enzyme complex becomes frozen in one of the intermediate complexes. Recent evidence in other laboratories has suggested that this complex may be an acyl intermediate. These researchers have been testing this hypothesis. Their evidence to date indicates that alpha-1-antitrypsin combines with trypsin in a 1:1 molar combination. During the process, a peptide is cleaved from alpha-1-antitrypsin. They have accumulated some evidence which suggests that the alpha-1-antitrypsin-trypsin complex is an acyl ester, as suggested by the hypothesis. The complex is alkaline-labeled and separates at pH 9.5 to yield an active enzyme and an inactive fragment of alpha-1-antitrypsin. The new C-terminal residue on alpha-1-antitrypsin appears to be a lysyl residue, suggesting that trypsin combines with a lysyl residue at the inhibitory site of alpha-1-antitrypsin.

The investigators are now performing further experiments to further document this hypothesis. In addition, they are exploring means of affinity labeling the inhibitory sites on alpha-1-antitrypsin so that the active site of the inhibitor can be sequenced.

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